Low serum total cholesterol concentrations and mortality in middle aged British men

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Abstract

***Objective*—To examine the relation between low serum total cholesterol concentrations and causes of mortality.**

***Design*—Cohort study of men followed up for an average of 14·8 years (range 13·5-16·0 years).**

***Setting*—One general practice in each of 24 British towns.**

***Subjects*—7735 men aged 40-59 at screening selected at random from the 24 general practices.**

***Main outcome measures*—Deaths from all causes, cardiovascular causes, cancer, and non-cardiovascular, non-cancer causes.**

***Results*—During the mean follow up period of 14·8 years there were 1257 deaths from all causes, 640 cardiovascular deaths, 433 cancer deaths, and 184 deaths from other causes. Low serum cholesterol concentrations (< 4·8 mmol/l), present in 5% (n=410) of the men, were associated with the highest mortality from all causes, largely due to a significant increase in cancer deaths (age adjusted relative risk 1·6 (95% confidence interval 1·1 to 2·3); < 4·8 *v* 4·8-5·9 mmol/l) and in other non-cardiovascular deaths (age adjusted relative risk 1·9 (1·1 to 3·1)). Low serum cholesterol concentration was associated with an increased prevalence of several diseases and indicators of ill health and with lifestyle characteristics such as smoking and heavy drinking. After adjustment for these factors in the multivariate analysis the increased risk for cancer was attenuated (relative risk 1·4 (0·9 to 2·0)) and the inverse association with other non-cardiovascular, non-cancer causes was no longer significant (relative risk 1·5 (0·9 to 2·6); < 4.8 *v* 4·8-5·9 mmol/l). The excess risks of cancer and of other non-cardiovascular deaths were most pronounced in the first five years and became attenuated and non-significant with longer follow up. By contrast, the positive association between serum total cholesterol concentration and cardiovascular mortality was seen even after more than 10 years of follow up.**

***Conclusion*—The association between comparatively low serum total cholesterol concentrations and excess mortality seemed to be due to preclinical cancer and other non-cardiovascular diseases. This suggests that public health programmes encouraging lower average concentrations of serum total cholesterol are unlikely to be associated with increased cancer or other non-cardiovascular mortality.**

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Introduction

There is concern that public health measures aimed at lowering mean total cholesterol concentrations in the population to reduce coronary heart disease may lead to increased mortality from non-cardiovascular causes. Low blood cholesterol concentrations have been associated with increased mortality from non-cardiovascular causes, particularly cancer.[1-17] Recent studies have also shown significant inverse associations between blood cholesterol concentrations and respiratory deaths other than cancer.[3 4] These findings suggest that a low blood cholesterol concentration may be a consequence of early disease, particularly cancer or chronic respiratory disease.

Several studies have explored these possibilities by excluding early deaths in the follow up period. In some studies the increased risk of cancer was attenuated or abolished[3-7 16 17] whereas in others the relation was not affected.[8-11 13-15] Other studies have shown low cholesterol concentrations to be associated with adverse lifestyle characteristics—for example, smoking and heavy drinking, socioeconomic status, presence of disease at screening, and poorer self reported health. Attention has been drawn to the possible confounding role of these factors in explaining the cholesterol-mortality relation.[1 2 4 18 19] Few studies, however, have explored the relation between blood cholesterol concentration and cancer and other non-cardiovascular mortality taking into account both lifestyle characteristics and morbidity at screening.

This paper examines the relation between blood cholesterol concentrations and mortality in a middle aged male British cohort taking into account the role of lifestyle characteristics, pre-existing disease, and biological indicators of morbidity.

Subjects and methods

The British regional heart study is a prospective study of cardiovascular disease involving 7735 men aged 40-59 selected from the age-sex registers of one group general practice in each of 24 towns in England, Wales, and Scotland. Criteria for selecting the towns, general practices, and subjects as well as the methods of data collection have been reported.[20] Research nurses administered a standard questionnaire to each man which included questions on smoking, alcohol intake, and medical history. Several physical measurements were made and non-fasting blood samples taken for measurement of biochemical and haematological variables. Serum total cholesterol concentrations were measured by a modified Liebermann-Burchard method on a Technicon SMA 12/60 analyser.[21] Body mass index (weight (kg) over height (m^2)) was used as an index of relative weight. Forced expiratory volume in one second was measured with a Vitalograph spirometer and was height standardised to 1·73 m, the average height of the men in this study.

The men were classified according to smoking status as never smokers, ex-smokers, and current smokers (1-19, 20, 21-39, and 40 or more cigarettes daily). Alcohol consumption was recorded by means of questions on frequency, quantity, and type. Heavy drinking was defined as taking more than six drinks daily. The longest held occupation of each man was

coded in accordance with the Registrar General's classification of occupations. The men were asked to indicate their usual pattern of physical activity and a score derived for each man based on the frequency and type (intensity).[22] The men were grouped into six broad categories based on their total score. Heart rate was determined from a three orthogonal lead electrocardiogram.

Pre-existing disease—The men were asked to recall a doctor's diagnosis of angina, myocardial infarction, stroke, diabetes, bronchitis, asthma, peptic ulcer, and several other disorders listed on the questionnaire. They were also asked details of any regular medical treatment, including use of antihypertensive drugs. The World Health Organisation (Rose) chest pain questionnaire was administered to all men at the initial examination[23] and a three orthogonal lead electrocardiogram recorded at rest. Men with pre-existing ischaemic heart disease included those with electrocardiographic evidence of possible or definite myocardial ischaemia or possible or definite myocardial infarction, those with angina or possible myocardial infarction on the WHO chest pain questionnaire, and those who recalled a doctor's diagnosis of angina or myocardial infarction.

Follow up—All men were followed up for all cause mortality and cardiovascular morbidity.[24] All deaths up to December 1993 were included in the study (average follow up 14·8 years; range 13·5-16·0 years), follow up being achieved for 99% of the cohort. Information on death was collected by means of "tagging" by the NHS registers in Southport (for England and Wales) and Edinburgh (for Scotland). Classification into deaths from cardiovascular and non-cardiovascular causes was based on the International Classification of Diseases (9th revision) codings on the death certificates.

Statistical methods—Cox's proportional hazards model was used to assess the relation between cholesterol concentrations and mortality, adjusting for the other risk factors.[25] The estimated hazard ratios (relative risks) for the four cholesterol concentration groups adjusted for the other risk factors were obtained fitting cholesterol as three dummy variables (for the four groups). Tests for trend were carried out fitting cholesterol in its original continuous form. In the adjustment, age, systolic blood pressure, heart rate, serum albumin concentration, forced expiratory volume in one second, and physical activity were fitted continuously and history of diabetes and use of antihypertensive treatment fitted as a 0,1 variable. Pre-existing ischaemic heart disease (none, evidence of ischaemic heart disease short of a myocardial infarction, and definite myocardial infarction), social class (manual, non-manual, armed forces), alcohol intake (none, occasional, light, moderate, and heavy), and cigarette smoking (never, former, and 1-19, 20, 21-39, and 40 or more daily) were fitted as categorical variables in the proportional hazards model. Body mass index was fitted as six levels (<20, 20-, 22-, 24-, 26-, and ≥28) because of the non-linear relation between it and mortality.[26]

TABLE I—*Death rates per 1000 person years (No of deaths) for specific causes of non-cardiovascular death*

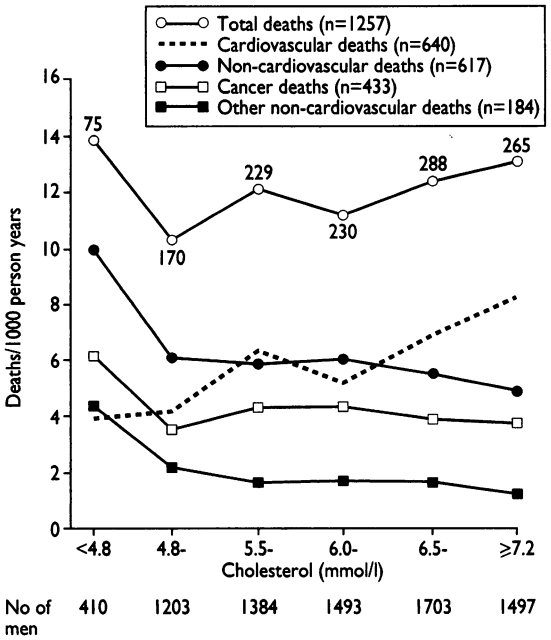
Serum cholesterol (mmol/l)	No of men	Cancer deaths				Non-cardiovascular and non-cancer deaths		
		Lung (152)	Digestive (124)	Other (157)	All (433)	Respiratory (82)	Other (102)	All (184)
<4·8	410	2·0 (11)	1·5 (8)	2·8 (15)	6·3 (34)	2·0 (11)	1·7 (9)	3·7 (20)
4·8-	1203	1·5 (24)	1·0 (16)	1·2 (20)	3·7 (60)	1·2 (20)	1·3 (21)	2·5 (41)
5·5-	1384	1·6 (31)	0·9 (17)	1·8 (34)	4·3 (82)	0·6 (11)	1·0 (18)	1·6 (29)
6·0-	1493	1·5 (30)	1·2 (24)	1·7 (36)	4·4 (90)	0·8 (17)	0·8 (16)	1·7 (33)
6.5-	1703	1·4 (33)	1·5 (36)	1·0 (23)	3·9 (92)	0·5 (12)	1·1 (25)	1·6 (37)
≥7·2	1497	1·1 (23)	1·1 (23)	1·4 (29)	3·6 (75)	0·5 (11)	0·6 (13)	1·2 (24)

Results

During the mean follow up period of 14·8 years (range 13·5-16·0 years) there were 1257 deaths from all causes among the 7690 men for whom serum total cholesterol estimations were available. Of these, 640 (51·0%) were due to cardiovascular disease (502 ischaemic heart disease, 64 stroke, and 74 other cardiovascular causes) and 617 men died of non-cardiovascular causes. Of these men, 433 (34·4%) died of cancer, 82 (6·5%) of respiratory disease, 27 (2·1%) as a result of accidents and violence, 25 (2·0%) of liver or other digestive diseases, 10 of diseases of the central nervous system (0·8%), 8 (0·6%) of renal failure, and 32 (2·5%) of other causes.

CHOLESTEROL AND ALL CAUSE MORTALITY

The men were initially divided into fifths of blood cholesterol concentration (<5·5, 5·5-5·9, 6·0-6·4, 6·5-7·1, and ≥7·2 mmol/l). But because of the particular interest in low cholesterol concentrations we further separated men with values below 5·5 mmol/l into two groups at centile points representing 5% and 20% of the total distribution (<4·8 and 4·8-5·4 mmol/l). Thus six groups are presented in the figure to show the death rates per 1000 person years for all causes, cardiovascular causes, all non-cardiovascular causes, and separately for cancer and other non-cardiovascular causes—namely, <4·8 (n=410), 4·8-5·4 (n=1203), 5·5-5·9 (n=1384), 6·0-6·4 (n=1493), 6·5-7·1 (n=1703), and ≥7·2 mmol/l (n=1497).



Death rates per 1000 person years for all causes, cardiovascular causes, all non-cardiovascular causes, and cancer and other non-cardiovascular causes by six serum cholesterol concentration groups

Serum cholesterol concentrations below 4·8 mmol/l were associated with the highest all cause mortality, which was attributable entirely to non-cardiovascular causes. Mortality was lowest in men with cholesterol concentrations of 4·8-5·4 mmol/l and thereafter increased slightly with increasing concentration. Cancer mortality was increased only in men with concentrations below 4·8 mmol/l; at higher concentrations there was no difference in mortality between the groups. An inverse relation with cholesterol concentration was seen with other non-cardiovascular causes (test for trend: P=0·0005).

Detailed analysis of specific causes of non-cardiovascular deaths (table I) showed excess deaths from lung cancer and cancer at sites other than the digestive tract in the low cholesterol concentration group

TABLE II—*Serum total cholesterol concentrations and lifestyle and biological factors and pre-existing disease.*

	Serum cholesterol (mmol/l)				
	<4·8 (n=410)	4·8-5·9 (n=2587)	6·0-7·1 (n=3196)	≥7·2 (n=1497)	Test for trend
Lifestyle factors:					
Mean age (years)	50·0	50·1	50·5	50·1	NS
No (%) current smokers	193 (47·1)	1063 (41·2)	1310 (41·1)	595 (39·9)	***
No (%) heavy drinkers	56 (13·7)†	274 (10·6)	337 (10·6)	162 (10·8)	NS
No (%) smokers and heavy drinkers	41 (10·0)	167 (6·5)	183 (5·7)	77 (5·2)	**
No (%) manual workers	263 (65·8)	1568 (62·6)	1818 (58·8)	754 (52·4)	***
No (%) inactive	40 (9·8)	229 (9·0)	273 (8·7)	140 (9·5)	NS
Biological factors:					
No (%) thin (body mass index (kg/m²) <20)	40 (9·8)	134 (5·2)	78 (2·4)	17 (1·1)	***
No (%) obese (body mass index (kg/m²) ≥28)	54 (13·2)	416 (16·1)	668 (20·9)	348 (23·2)	***
Mean systolic blood pressure (mm Hg)	140·0	144·1	146·0	146·8	***
Mean heart rate (beats/min)	69·6	70·1	70·6	71·6	***
Mean forced expiratory volume in one second (l)	3·28	3·30	3·33	3·34	NS
Mean albumin (g/l)	43·1	44·1	44·7	45·3	***
Cardiovascular related disease:					
No (%) with pre-existing ischaemic heart disease	92 (22·4)	613 (23·7)	804 (29·1)	424 (28·3)	***
No (%) with diabetes	6 (1·5)	40 (1·5)	51 (1·6)	20 (1·3)	NS
No (%) on antihypertensive treatment	13 (3·2)	95 (3·7)	160 (5·0)	107 (7·2)	***
Other disease, treatment, and anaemia:					
No (%) with bronchitis	102 (24·9)	496 (19·5)	524 (16·4)	262 (17·5)	***
No (%) with asthma	17 (4·2)	100 (3·9)	116 (3·6)	52 (3·5)	NS
No (%) with peptic ulcer	59 (14·4)	291 (11·4)	331 (10·4)	152 (10·2)	*
No (%) with gall bladder disease	9 (2·2)	56 (2·1)	50 (1·6)	17 (1·1)	*
No (%) on treatment	145 (36·4)†	729 (28·1)	880 (27·5)	446 (29·8)	NS
No (%) anaemic (packed cell volume <0·40)	52 (13·4)	154 (6·6)	119 (3·9)	44 (3·1)	***

†Test for low cholesterol concentration (<4·8 mmol/l) *v* the rest (P<0·05).
*P<0·05. **P<0·01. ***P<0·0001. NS=non-significant.

TABLE III—*Age adjusted and adjusted relative risk (95% confidence interval) for all deaths, cancer, other non-cardiovascular, and cardiovascular deaths by serum cholesterol concentration*

Serum cholesterol (mmol/l)	Age	Adjusted for A	Adjusted for B
Total deaths (n=1203):			
<4·8	1·2	1·1 (0·9 to 1·6)	1·1 (0·9 to 1·4)
4·8-	1·0	1·0	1·0
6·0-	1·0	1·0 (0·9 to 1·1)	1·1 (0·9 to 1·2)
≥7·2	1·2	1·2 (1·0 to 1·4)	1·3 (1·1 to 1·5)
Cancer deaths (n=413):			
<4·8	1·6	1·5 (1·0 to 2·2)	1·4 (0·9 to 2·0)
4·8-	1·0	1·0	1·0
6·0-	1·0	1·0 (0·8 to 1·2)	1·0 (0·8 to 1·2)
≥7.2	0·9	1·0 (0·7 to 1·3)	1·0 (0·8 to 1·3)
Other non-cardiovascular deaths (n=174):			
<4·8	1·9	1·7 (1·0 to 2·9)	1·5 (0·9 to 2·6)
4·8-	1·0	1·0	1·0
6·0-	0·8	0·8 (0·6 to 1·1)	0·9 (0·7 to 1·3)
≥7·2	0·6	0·6 (0·4 to 1·0)	0·7 (0·4 to 1·2)
Cardiovascular deaths (n=616):			
<4·8	0·7	0·7 (0·4 to 1·1)	0·7 (0·4 to 1·1)
4·8-	1·0	1·0	1·0
6·0-	1·1	1·1 (0·9 to 1·3)	1·1 (0·9 to 1·3)
≥7·2	1·5	1·6 (1·3 to 2·0)	1·6 (1·3 to 2·0)

Analysis included 7415 men with complete data on all covariates: serum cholesterol <4·8 mmol/l, n=392; 4·8-5·9 mmol/l, n=2501; 6·0-7·1 mmol/l, n=3090; ≥7·2 mmol/l, n=1432. Cholesterol concentrations 4·8-5·9 mmol/l used as reference group.
A=Age, social class, smoking, alcohol intake, and physical activity.
B=A plus body mass index, systolic blood pressure, forced expiratory volume in one second, heart rate, serum albumin concentration, pre-existing ischaemic heart disease, history of diabetes, and use of antihypertensive drugs.

(<4·8 mmol/l). For other non-cardiovascular causes an inverse association was seen for both respiratory (P=0·002) and non-respiratory causes (P=0·06).

LIFESTYLE AND BIOLOGICAL FACTORS AND CARDIOVASCULAR RELATED DISEASE

Because of the specific interest in men with low cholesterol concentrations, and to simplify presentation, men with concentrations between 4·8 and 5·9 mmol/l and those with concentrations of 6·0-7·1 mmol/l were combined. Thus four groups are presented (<4·8, 4·8-5·9, 6·0-7·1, and ≥7·2 mmol/l), representing the 5th, 20th, 40th, and 80th centiles of the distribution. Table II shows the relation between serum cholesterol concentration and lifestyle factors, biological factors, and cardiovascular related diseases known to be associated with mortality by the four groups of cholesterol concentration. There was little association with age, physical activity, and a history of diabetes. Men with low cholesterol concentrations were more likely to be current smokers, heavy drinkers, or both, and more likely to be manual workers. They included the highest proportion of men with a body mass index below 20, men with slightly poorer lung function (forced expiratory volume in one second), and men with lower serum albumin concentrations. These factors are known to be influenced by ill health and are strongly associated with non-cardiovascular mortality.[26-28] These men also had the lowest mean systolic blood pressure and heart rate and included the lowest proportion with pre-existing ischaemic heart disease or taking antihypertensive treatment.

MULTIVARIATE ANALYSIS

To illustrate the separate effects of lifestyle factors, biological factors, and possible indicators of ill health on the cholesterol-mortality relation we adjusted for potential confounders in three cumulative stages: age, lifestyle factors, and biological factors and possible indicators of ill health. Table III shows the successive adjusted relative risk for all causes of death, cardiovascular causes, and cancer and other non-cardiovascular causes for the four cholesterol concentration groups, the group with concentrations of 4·8-5·9 mmol/l being taken as the reference group.

Adjustment for lifestyle factors reduced the increased risk for all cause mortality in the low cholesterol concentration group. Further adjustment for biological factors and indicators of ill health increased the risk in the high cholesterol concentration groups and a positive association was seen (test for trend: P<0·001). The excess risk for cancer mortality and other non-cardiovascular mortality in men with cholesterol concentrations <4·8 mmol/l was slightly reduced after adjustment for lifestyle factors, but the excess risk remained significant. After further adjustment for biological factors and indicators of ill health the increased risk for cancer was attenuated (relative risk 1·4; 95% confidence interval 0·9 to 2·0) and the inverse association with other non-cardiovascular causes of death was still present but no longer significant (P=0·16). A positive association was seen with cardiovascular disease even after the full adjustment (P<0·0001).

PRE-EXISTING DISEASE AND INDICATORS OF ILL HEALTH

Men with low blood cholesterol concentrations (<4·8 mmol/l) had the highest prevalence of regular treatment, bronchitis, asthma, peptic ulcer, and gall bladder disease and included a high proportion of men who were anaemic (table II). However, the increased risk of cancer and of other non-cardiovascular deaths in the low cholesterol group remained after these men were excluded.

EARLY AND LATE FOLLOW UP

In order to investigate the hypothesis of the effect of preclinical cancer and of other non-cardiovascular disease on serum total cholesterol we examined the relation between blood cholesterol concentration and different types of mortality by three separate follow up periods—namely, the first five years, the subsequent five to 10 years, and more than 10 years (table IV).

The significant increase in total mortality in the low cholesterol concentration group was seen only in the first five years and was due to a pronounced increase in cancer and non-cardiovascular causes. The increased mortality from cancer in men with low cholesterol concentrations was particularly noticeable in the first five years. The risk attenuated with increasing follow up and disappeared after 10 years. For other non-cardiovascular mortality the excess risk was most

TABLE IV—*Relative risk (95% confidence interval) of total, cancer, other non-cardiovascular, and cardiovascular mortality adjusted for age, social class, smoking, alcohol intake, physical activity, body mass index, systolic blood pressure, forced expiratory volume in one second, heart rate, serum albumin concentration, pre-existing ischaemic heart disease, history of diabetes, and use of antihypertensive treatment by time of follow up. Analysis based on 7415 men with complete data on all covariates*

	Follow up period (years)		
Serum cholesterol (mmol/l)	≤5·0	5·1-10·0	>10·0
Total deaths:	(n=271)	(n=438)	(n=494)
<4·8	1·7 (1·1 to 2·7)	1·2 (0·8 to 1·7)	0·8 (0·5 to 1·3)
4·8-	1·0	1·0	1·0
6·0-	1·1 (0·7 to 1·5)	1·1 (0·9 to 1·3)	1·0 (0·8 to 1·2)
≥7·2	1·5 (1·1 to 2·1)	1·4 (1·0 to 1·8)	1·1 (0·9 to 1·4)
Cancer deaths:	(n=81)	(n=158)	(n=174)
<4·8	2·5 (1·2 to 5·0)	1·3 (0·7 to 2·6)	1·0 (0·4 to 2·0)
4·8-	1·0	1·0	1·0
6·0-	1·0 (0·6 to 1·7)	1·1 (0·8 to 1·6)	1·0 (0·7 to 1·3)
≥7·2	0·9 (0·4 to 1·8)	1·2 (0·8 to 2·0)	0·9 (0·6 to 1·4)
Other non-cardiovascular deaths:	(n=48)	(n=59)	(n=67)
<4·8	2·3 (1·1 to 5·2)	0·9 (0·3 to 2·7)	1·4 (0·5 to 3·7)
4·8-	1·0	1·0	1·0
6·0-	0·9 (0·5 to 1·8)	0·7 (0·4 to 1·2)	1·2 (0·7 to 2·2)
≥7·2	1·2 (0·5 to 2·9)	0·4 (0·1 to 1·0)	0·9 (0·4 to 1·9)
Cardiovascular deaths:	(n=142)	(n=221)	(n=253)
<4·8	0·6 (0·2 to 1·6)	1·1 (0·5 to 2·1)	0·5 (0·2 to 1·0)
4·8-	1·0	1·0	1·0
6·0-	1·2 (0·8 to 1·8)	1·3 (0·9 to 1·8)	1·0 (0·7 to 1·3)
≥7·2	1·9 (1·2 to 3·0)	1·9 (1·4 to 2·7)	1·3 (0·9 to 1·8)

noticeable in the first five years and was attenuated with longer follow up. In the 5-10 year follow up period an inverse association remained and the result of a test for trend was significant ($P<0·05$). After 10 years of follow up there was no significant inverse relation, though men with low cholesterol concentrations showed the highest risk. For cardiovascular mortality a significant positive association was seen in all follow up periods (test for trend: $P<0·0001$, $P<0·0001$, $P=0·002$ for the three periods respectively), though there was some attenuation after 10 years.

Discussion

An early report from the British regional heart study showed no association between cholesterol concentration and mortality,[29] but men with very low cholesterol concentrations (<4·8 mmol/l) had not been separated from the rest of the lowest fifth of values (<5·5 mmol/l). In this analysis serum total cholesterol concentration was associated with a significant increase in mortality only at readings below 4·8 mmol/l, men in this group comprising 5% (n=410) of all men in the study. The excess mortality was largely due to cancer and other non-cardiovascular causes.

The increased risk with cholesterol concentrations below 4·8 mmol/l is consistent with the findings of many American studies, in which cholesterol concentrations below 4·2-4·8 mmol/l were associated with increased mortality.[1-3] The varying absolute concentrations of serum total cholesterol in the different studies at which the adverse association with mortality occurs may relate to the distribution of blood cholesterol concentrations in the population. In the urban Shanghai Chinese study[30] the mean total cholesterol concentration was 4·2 mmol/l. By contrast, in the British regional heart study the mean total cholesterol concentration was 6·3 mmol/l. The Chinese study found no association between the serum total cholesterol concentration and total cancer deaths within the study range of 3·8-4·7 mmol/l and overall cancer mortality was not particularly high. This suggests that the excess deaths seen in the low cholesterol concentration group in other studies may be due to the cholesterol concentration being lowered as a consequence of disease rather than low concentrations leading to excess mortality.

CANCER MORTALITY

Excess risk was still seen for cancer in this study after adjustment for a wide range of lifestyle and biological factors and indicators of morbidity, though it was not significant. It has been suggested that the increased risk may be due to preclinical cancer, and several studies have examined this by excluding deaths in the early years of follow up. In several studies the risk of cancer was attenuated with longer follow up,[3-7 16 17] though in some studies the increased risk remained.[8-11 13-15] In the British regional heart study the risk was greatly attenuated when deaths in the first five years were excluded, and the excess risk disappeared after exclusion of the first 10 years. This is consistent with the findings of several recent large studies.[3 4] The increased risk of cancer was particularly pronounced in the first five years and suggests that preclinical cancer may explain a major part of the excess mortality in men with comparatively low blood cholesterol concentrations. In many studies that have found a positive association after exclusion of early follow up data follow up has been less than 10 years and many have not adjusted for other indicators of ill health.

OTHER NON-CARDIOVASCULAR MORTALITY

Fewer studies have examined the relation between cholesterol concentrations and other non-cardiovascular, non-cancer deaths. In those that have, low cholesterol concentration has been associated with excess deaths largely due to causes related to smoking or heavy drinking, in particular respiratory and liver diseases.[3 4 12 30] We found that men with a low cholesterol concentration had high rates of smoking; a higher prevalence of bronchitis; slightly poorer lung function; included a higher proportion of thin men (body mass index <20), which may reflect weight loss; and had a higher prevalence of several indicators of ill health—for example, regular medication, low serum albumin concentration, and anaemia. The inverse association seen for other non-cardiovascular causes of death, though present, was attenuated and became non-significant after adjustment for lifestyle, biological factors, and indicators of morbidity. The increased risk of other non-cardiovascular death in the low blood cholesterol concentration group was seen most clearly in the first five years of follow up and was greatly attenuated after exclusion of men who died within the first five years. Though an inverse association between cholesterol concentration and other non-cardiovascular mortality was observed in the 5-10 year period, this was due to lower risks in men in the higher cholesterol concentration categories, who are particularly prone to coronary heart disease.

Many studies have shown excess mortality from respiratory disease in the low cholesterol concentration group which persisted even after excluding deaths in early follow up.[3 4] This was also seen in this study (data not shown). However, many respiratory diseases are chronic and do not necessarily result in death early in follow up. There is evidence that respiratory diseases are associated with lower cholesterol concentrations,[31] and our finding of an increased prevalence of bronchitis and slightly higher rates of asthma and poorer lung function in the low cholesterol concentration group is consistent with this. Our findings suggest that the excess deaths are due to pre-existing chronic disease and that low cholesterol concentration may be a marker of the chronic disease process.

There were very few deaths from accidents or violence in this study and no association was seen with the serum total cholesterol concentration. Deaths relating to non-cancerous digestive disorders—for example, liver disease—were few (n=19) but there was a tendency for these to be concentrated in the low cholesterol concentration group. Heavy drinking, which may cause liver disease, has been shown to be associated with low cholesterol concentration,[23] and

Key messages

- Present health policies encourage lower blood cholesterol concentrations
- There are fears that lowering blood cholesterol concentrations may increase the risk of cancer and other non-cardiovascular deaths
- The association between the excess risk of cancer and other non-cardiovascular disease and lower blood cholesterol concentrations (<4·8 mmol/l) is produced by preclinical cancer, chronic ill health, smoking, and heavy drinking
- In this series excess deaths in men with lower cholesterol concentrations occurred in the first five years of follow up
- There is no valid reason for changing current policies on lowering blood cholesterol concentrations

the inverse association between cholesterol concentration and liver disease[3 30] may relate to heavy drinking.

IMPLICATIONS

Our findings are consistent with a recent systematic review of published data. That review concluded that in cohort studies of subjects in community settings the association of low serum cholesterol concentration with excess mortality from lung cancer, haemopoietic cancers, suicide, chronic bronchitis, and chronic liver and bowel disease is satisfactorily explained by early disease or by factors that cause the disease, lowering the serum cholesterol concentration.[2] Low cholesterol concentration was defined as below about 5 mmol/l, affecting about 6% of people in Western populations.

That same review showed that, in randomised trials designed to lower the serum total cholesterol concentration, apart from a few deaths attributed to adverse effects of specific treatments there was no evidence of increased mortality from any cause arising from a reduction in the cholesterol concentration.[2] The fear that encouraging populations towards a lower mean cholesterol concentration would result in an increase in non-cardiovascular mortality appears to be without foundation.[32 33] It has been emphasised that programmes designed to lower blood cholesterol concentrations in the general population through appropriate dietary means have the merit that the recommended eating patterns may be beneficial in relation to other chronic diseases as well as coronary heart disease.[34] Our study provides further evidence that in the British population there is no good reason to abandon this approach.

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ONE HUNDRED YEARS AGO

CYCLES FOR INVALIDS.

The possible uses of the cycle have not yet been dreamt of. The cumbersome Bath chair for invalids is giving place to the Coventry chair, which consists of a light wicker chair mounted as a tricycle driven from behind. In this easy little carriage an invalid can be trundled about the country lanes at the rate of five or six miles an hour, enjoying the breezes and the sunshine and the invigorating pleasure of change of scene at very small expense. Many country doctors have long been accustomed to pay their visits on a tricycle; but we hear now of a cycle cab used by a metropolitan doctor, which is driven by two youths, one behind and the other in front. By this method fatigue is avoided and the expenses of the stable abolished.

(*BMJ* 1895;ii:546.)